PCT

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification [5] : A61K

A2

(11) International Publication Number: WO 92/19209

(43) International Publication Date: 12 November 1992 (12.11.92)

(21) International Application Number: PCT/US92/02692

(22) International Filing Date: 3 April 1992 (03.04.92)

(30) Priority data:
693,732 30 April 1991 (30.04.91) US

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(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), NO, SE (European patent).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: TASTE-MASKED MEDICAMENTS AND THEIR PREPARATION

(57) Abstract

A taste-masked solid medicament such as an aspirin tablet or the like in which the taste-masking means is a thin cellulose ester film formed of the dried coating of an aqueous plasticized cellulose ester dispersion. The film constitutes no more than about 1 part percent of the film coated medicament.

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TASTE-MASKED MEDICAMENTS AND THEIR PREPARATION

This invention relates to taste-masking of solid medicaments, particularly by enveloping them in a taste-masking polymer film coating.

Therapeutic formulations designed for oral administration often contain active ingredients which have an unpleasant taste. For instance, many drugs produce a bitter or acrid sensation when taken by mouth.

Various techniques are known for counteracting the disagreeable taste of medicinal products. Perhaps the oldest approach is to include a flavoring agent in the formulation to overpower the taste of the offending component. Both solid and liquid medicaments can be taste-masked in this manner.

In the case of a solid medicament, taste-masking is commonly effected by coating the medicament with a taste blocking layer. This can be something as simple as a sugar coating which dissolves to provide a pleasant taste during the interval between ingestion and swallowing of the medicament. More recently, the pharmaceutical industry has focused its attention on coatings produced from film-forming polymers and considerable effort has been devoted and continues to be devoted along this line of approach for taste-masking of solid dosage forms.

A new development in polymeric taste-masking films is disclosed in U. S. Patent No. 4,851,226 to Julian et al. These films are formed of a blend of a cellulose ester and polyvinylpyrrolidone (PVP) applied to a medicament such as acetyl-p-aminophenol (acetaminophen or APAP) from an organic solvent solution of the polymers. The purpose of the PVP, which is water soluble, is to temper the hydrophobic character of the cellulose ester and thereby control the drug release rate of the medication. According to the patent, a film coating may be designed so that the medicine is released relatively rapidly or in a sustained released mode. When rapid

release is desired, the proportion of PVP in the film coating is from about 12% to 20% by weight. If used alone, however, the patentees found that the cellulose ester coating would not provide adequate bioavailability of the active ingredient at the specified coating levels of 5% to 20% by weight. This is clearly evident from Figure 1 of the patent depicting in graphic form the dissolution rate of APAP in simulated gastric fluid at a coating level of 17.5% by weight and which the percent of PVP in the coating blend varied from 0% to 25% by weight. As will be noted, at 0% PVP in the film coating drug release amounted to only 40% after 40 minutes.

The chief problem with the coatings of the Julian et al. patent is that they are applied from an organic solvent solution of the film-forming resin. Such solvents tend to be toxic and/or flammable thereby posing a hazard to personnel and operators. Also, organic solvents are pollutants, necessitating the installation of expensive and complex solvent recovery systems to meet environmental regulations. Furthermore, traces of residual solvent may remain in the treated medicament giving use to a potential health threat.

In accordance with the present invention solid medicaments can be effectively taste-masked with a film envelope consisting essentially of a cellulose ester applied from a latex dispersion of the ester, while maintaining rapid release of active ingredients. The provision of such taste-masked medicaments constitutes the main advantage and purpose of the invention. Other advantages and purposes will become apparent in the ensuing description.

The advantages and purposes aforesaid are realized by employing as the source of the cellulose ester film envelope, an ultra-thin coating formed of the dried residue of an aqueous plasticized dispersion of the cellulose ester. Remarkably, taste-masking of aspirin tablets at coating levels significantly below about 0.4%

have been realized while also exhibiting dissolution profiles similar to uncoated controls.

Figure 1 is a graph of percent dissolution versus time for aspirin tablets (acetylsalicylic acid - ASA) coated with the ultra-thin cellulose ester films made in accordance with the invention and the uncoated core control.

In Figure 1 the symbols have the following meaning:

Uncoated Cores
CA Latex, 5 Min.
CA Latex, 10 Min.

Figure 2 is a graph of percent dissolution versus time for ASA tablets coated with the ultra-thin cellulose ester films of the invention, for ASA tablets similarly coated with the cellulose ester/PVP blend of U. S. Patent No. 4,851,226 to Julian et al., and for the uncoated core control.

In Figure 2 the symbols have the following meaning:

Uncoated Cores
CA/PVP Latex, 5 Min.
CA/PVP Latex, 10 Min

The aqueous plasticized cellulose ester dispersion used in the practice of the invention is a known chemical entity. Commonly referred to as a cellulose ester latex, it is prepared by dissolving the polymer in a suitable organic solvent, dispersing the resulting solution in an aqueous phase, homogenizing, and evaporating the solvent. To the resulting latex is added an appropriate plasticizer.

Cellulose ester latex systems have previously been

investigated as a film coating material for controlled release drug products. So far as is known, however, there has been no recognition or appreciation by the pharmaceutical community that cellulose ester latex dispersions would have application to taste-masking using the ultra-thin coating technique as set forth herein.

For a brief description of cellulose ester latex and its use in the fabrication of controlled drug delivery membranes, see Bindschaedler et al. Proceed. Intern. Symp. Control. Rel. Bioact. Mater 12, (1985).

Illustrative of the cellulose ester latexes suitable for producing the ultra-thin coatings of the invention are latexes made from cellulose acetate, cellulose acetate butyrate and cellulose acetate phthalate.

Cellulose ester polymers are manufactured and sold commercially by a number of suppliers of industrial chemicals, for example, the Eastman Kodak Company, Kingsport, Tenn.

Examples of suitable plasticizers for cellulose aqueous dispersions include triacetin, diacetin and triethylcitrate.

As understood herein, medicament can be, for example, granules, tablets including tablets of the compressed coated granules of drugs such as aspirin (ASA), acetaminophen, and ibuprofen.

The ultra-thin, taste-masking films of the invention are conveniently produced by coating the solid medicament substrate with an aqueous cellulose acetate dispersion in which the preferred plasticizer is triacetin. The triacetin is added to the dispersion and the mixture thoroughly mixed. In general, the amount of plasticizer ranges by weight from about 50% to about 150%, preferably from about 30% to 120%, optimally about 100% of the solids content of the dispersion. A cellulose acetate aqueous dispersion having a solids content of by weight of from about 28% to 32% is available from the FMC Corporation under the designation CA398-10 latex dispersion.

The ultra-thin, taste-masking cellulose films of the invention are applied to the solid medicament in a known manner and with standard pharmaceutical coating equipment. Coating is normally carried out by spraying in a pan or in a fluidized bed.

Solids content of the aqueous cellulose ester coating formulation plus plasticizer is in the neighborhood of from about by weight 10% to about 30%, preferably 15% to 20%. In the final dried coating, the amount of plasticizer present in the film coating ranges by weight from about 30% to about 60%.

As previously pointed out, effective taste-masking of standard pharmaceutical tablets such as an aspirin

can be realized with the ultra-thin cellulose ester film coatings of the invention at coating levels of about 0.4% by weight based on total solid dosage form weight. Other types of solid dosage forms such as granules may require somewhat higher coating levels. So far as has been determined, overall coating levels will vary from about 0.3% to about 1.0% by weight for effective taste-masking.

The amount of coating applied to the substrate can be controlled in known manner such as solids content of the coating dispersion and contact times.

The following examples, that is, procedures and test data tables illustrate the invention in further detail. Throughout this specification and claims, all parts and percentages are by weight unless otherwise indicated.

COATING FORMULATIONS

Formula #1

Ingredients	% Wet*	% in Dry Film
Cellulose acetate latex (29.0% solids)**	25.86	50.0
Triacetin	7.50	50.0
Water	66.64	----
	100.00	100.0

Formula #2

Ingredients	% Wet*	% in Dry Film
Cellulose acetate latex (29.0% solids)	21.98	42.5
Triacetin	6.38	42.5
Polyvinylpyrrolidone (PVP)***	2.25	15.0
Water	69.39	----
	100.00	100.0

* 15 % solids concentration in coating formulation

** CA398-10, FMC Corporation

***Kolidon[R] 30, BASF

COATING CONDITIONS:

Constant Conditions:

The following conditions were held constant for both batches.

Coating Equipment	AccelaCota 24 inch pan
Batch Size	10 kg ASA cores
Inlet Temperature Set	170 - 175°F
Pump Type	Peristaltic
Nozzle Size	1.0 mm
Atomizing Pressure	25 psi
Spray Rate	16 ml/min/gun

Batch #1 (ASA 325 mg coated with coating solution #1: CA latex)

Actual Inlet Temp. (°C)	63 - 67
Exhaust Temp. (°C)	37 - 43
Bed Temp. (°C)	34 - 42

Batch #2 (ASA 325 mg coated with coating solution #2: CA latex with PVP

Actual Inlet Temp. (°C)	62 - 66
Exhaust Temp. (°C)	38 - 41
Bed Temp. (°C)	36 - 42

Uncoated aspirin (ASA) cores and coated ASA tablet physical properties data are presented in Table I. It can be seen from the table that after five minutes of coating, ASA tablets coated with CA latex without PVP are exhibiting a 0.41% weight gain as compared to the 0.38% weight gain for the ASA tablets coated with CA latex with PVP. No detectable film could be measured at five minutes for coated ASA tablets without PVP, whereas a film (thickness) of 0.01 mm was measured for ASA tablets coated with CA latex with PVP. When the coated tablets were tasted after only five minutes coating, the masking of the acid taste of aspirin was clearly better for the ASA tablets without PVP in the film relative to

the ASA tablets with PVP in the film.

Julian et al. in U.S. Patent No. 4,851,226 state that PVP, a water-soluble polymer, is required to provide release of the drug acetaminophen from granules/-tablets coated with cellulose acetate applied from a solvent system. Dissolution analysis was performed on the coated tablets of this invention to determine if PVP was required to facilitate release of aspirin from tablets coated with cellulose acetate applied from an aqueous latex dispersion. The dissolution testing was performed using USP Apparatus 1 (Basket) at 50 rpm with 500 ml of 0.05M acetate buffer, pH 4.5. The samples were analyzed on a Beckman DU-7 UV/Vis spectrophotometer. The dissolution analysis results are presented in Table II and Figures 1 and 2.

Turning to the drawing, it can be seen from Figure 1 that the dissolution profile of ASA tablets coated with ultra-thin CA latex are essentially identical to the control ASA cores and that ASA release as depicted in Figure 2 was faster than for tablets coated with the CA latex/PVP blends of U.S. Patent 4,851,226 to Julian et al. Moreover, it was found that ASA tablets coated with CA latex without PVP exhibited superior taste-masking compared to tablets coated with CA latex/PVP blend at approximately identical coating levels.

Clearly, there is no advantage in using PVP to provide water solubility as claimed by Julian et al. since:

1. More effective taste-masking is realized at lower coating levels using CA latex without PVP relative to CA latex with PVP.

2. Dissolution analysis (ASA release) was more rapid for aspirin tablets coated solely with CA latex than with the CA latex/PVP blend.

TABLE I

TABLET PROPERTIES:

Uncoated ASA Cores

Physical Properties		Weight Variation (N=400)	
Thickness (mm, N=10)	4.27	Average wt. (mg)	-368.0
Dis. Time (sec, USP XXII for uncoated tabs)	- 50	St. Dev. (mg)	- 4.1
		Coeff. of Wt. Var. (%)	- 1.12
		Maximum wt. (mg)	-378
		Minimum wt. (mg)	-357

Coated ASA Tablets (post drying, 35°C/30 min)

Batch #1 (ASA 325 mg tablets coated with coating solution #1: CA latex)

Physical Properties	Init.	5 min	10 min	15 min
Thickness (mm, N=3)	- 4.27	4.25	4.30	4.29
Dis. Time (sec, N=3, USP XXII for uncoated tabs)	-25	32	48	63

Weight Variation (N=25)	Init.	5 min	10 min	15 min
Average wt. (mg)	- 367.6	369.1	369.9	371.2
St. Dev. (mg)	- 3.3	2.6	4.0	3.4
Coeff. of Wt. Var. (%)	- 0.89	0.71	1.07	0.92
Maximum wt. (mg)	- 375	375	378	375
Minimum wt. (mg)	- 360	364	361	363

TABLE I - Continued

TABLET PROPERTIES:

Batch #2 (ASA 325 mg tablets coated with coating solution #2: CA latex with PVP)

Physical Properties	Init.	5 min	10 min	15 min
Thickness (mm, N=3)	- 4.27	4.29	4.27	4.28
Dis. Time (sec, N=3, USP XXII for uncoated tabs)	- 25	33	25	38

Weight Variation (N=25)	Init.	5 min	10 min	15 min
Average wt. (mg)	- 367.6	369.0	368.6	370.3
St. Dev. (mg)	- 3.3	4.4	3.6	4.3
Coeff. of Wt. Var. (%)	- 0.89	1.19	0.99	1.15
Maximum wt. (mg)	- 375	378	378	378
Minimum wt. (mg)	- 360	361	364	363

TABLE II

Dissolution Profile of Coated Aspirin Tablets - Taste Masking Study

Mean % Aspirin in Solution ± S.D.

Cellulose Acetate Latex Coating (Batch 1)

Time (min)	Cores (n=18)	5 min CA Latex (n=3)	10 min CA Latex (n=3)
5	21 ± 5.2	22 ± 6.4	39 ± 11.0
10	46 ± 9.5	42 ± 12.5	62 ± 15.6
15	66 ± 10.7	61 ± 14.2	78 ± 14.2
30	94 ± 5.7	91 ± 12.1	96 ± 5.0

Cellulose Acetate Latex With PVP (Batch 2)

Time (min)	Cores (n=18)	CA Latex w/ PVP (n=3)	CA Latex w/ PVP (n=3)
5	21 ± 5.2	13 ± 0.6	30 ± 8.1
10	46 ± 9.5	27 ± 3.2	55 ± 6.1
15	66 ± 10.7	47 ± 9.0	77 ± 4.7
30	94 ± 5.7	74 ± 10.5	100 ± 1.2

CLAIMS:

1. A taste-masked, solid medicament in which the taste-masking agent is a cellulose ester film enveloping the medicament, and of sufficient thickness to act as a taste-masking barrier without interfering with the release of active ingredients from the medicament, the said film characterized by the dried residue of an aqueous plasticized cellulose ester and constituting no more than 1.0 weight percent of the film coated medicament.

2. The medicament of claim 1 characterized in that the film envelopment constitutes no more than 0.3 weight percent of the medicament.

3. The medicament of claim 1 characterized in that the plasticizer is present in the film in an amount of 33% weight percent to 60%.

4. The medicament of claim 1 characterized in that the plasticizer is triacetin.

5. A taste-masked disagreeable solid medicament enveloped in a cellulose acetate film characterized by the dried coating of an aqueous cellulose acetate dispersion, the said film containing by weight from 33% to 60% of triacetin plasticizer.

6. The composition of claim 5 characterized in that the amount of plasticizer is by weight 50%.

7. The composition of claim 5 characterized in that the disagreeable tasting medicament is selected from the class consisting of aspirin, acetaminophen and ibuprofen.

8. The composition of claim 7 characterized in that the medicament is in the form of granules, tablets or compressed coated granules.

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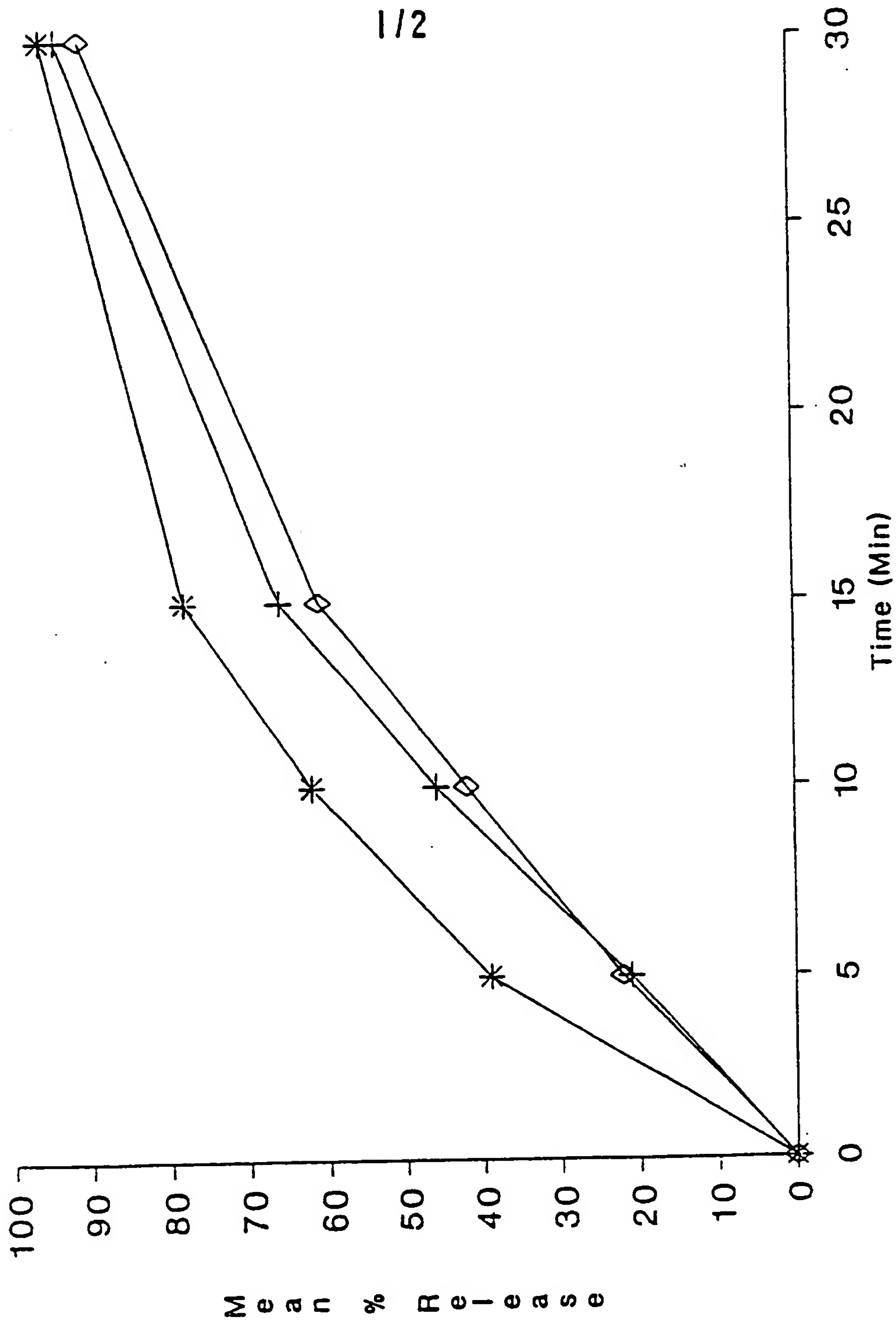
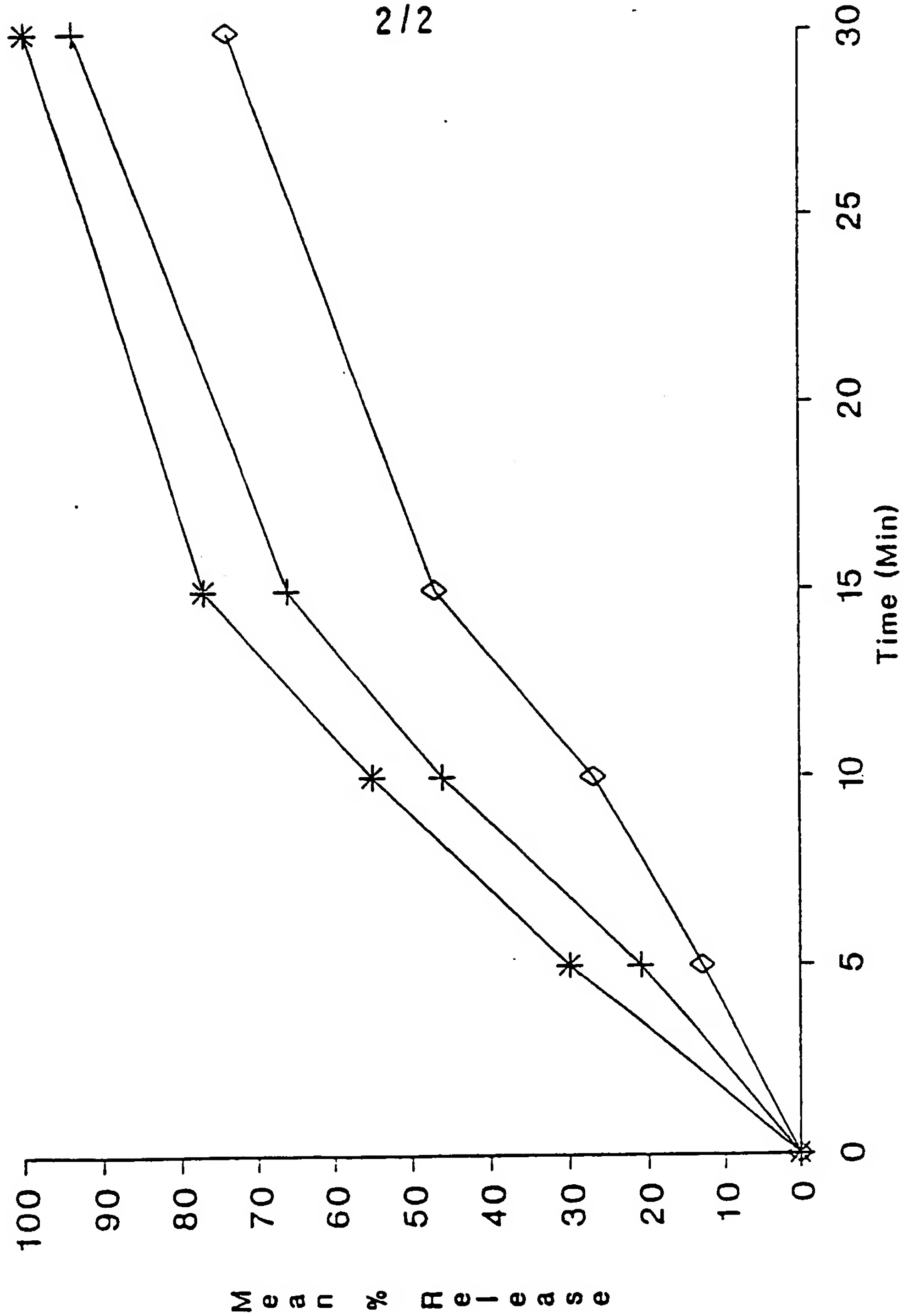
Figure 1


Mean % Release
0
10
20
30
40
50
60
70
80
90
100
Time (Min)
0
5
10
15
20
25
30

2/2

Figure 2


Mean % Release
100
90
80
70
60
50
40
30
20
10
0
Time (Min)
0
5
10
15
20
25
30